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Your Annual COVID-19 Vaccine Booster Could Be A Pill Or A Spray

Vaxart And Altimmune Set For Readouts

by Andrew McConaghie

A COVID-19 vaccine in a pill being developed by Vaxart and a nasal spray from Altimmune could offer convenience and maybe even superior immunity compared to injections.

While the majority of the world's population is still waiting for their first COVID-19 vaccine, many biopharma companies are looking ahead at how to make follow-up boosters more convenient.

Pfizer/BioNTech and Moderna's mRNA-based vaccines have established themselves as the big breakthrough of the last 12 months, but an entirely different approach could also revolutionize the field.

Intramuscular injections could be replaced by a pill or a spray, with several novel candidates now in early to mid-stage development, including oral candidates from *Vaxart* and *ImmunityBio* and nasal COVID-19 vaccines from both *Altimmune* and *AstraZeneca*'s partners Oxford University.

This week has seen interest in Vaxart's approach hit a new peak: the company's share price spiked up by 37% after it announced it would present new data on its candidate VXA-CoV2-1 on 3 May comparing its T-cell responses with those of other vaccines plus new antibody data.

The success of many oral and nasal vaccines for diseases such as polio and flu (eg, AstraZeneca/MedImmune's Flumist), has bolstered these companies' belief that COVID-19 could be targeted in a similar way.

Vaxart and Altimmune are looking to the likely booster market in developed nations, but also see

the potential for their vaccines in the first line. A pill or spray stable at room temperature could be transformative in the fight against COVID-19, especially in developing countries where lack of health infrastructure needed for refrigerated vaccines remains a big challenge.

Mucosal Immunity - A Better Barrier To Infection

In addition to convenience, oral and nasal vaccine candidates have other potential advantages in that they elicit immune response in a different way to subcutaneous or intramuscular vaccines.

In subcutaneous or intramuscular vaccines, the primary immune response is systemic humoral immunity, in which B-cells generate antibodies (IgG) against the pathogen in the blood. They tend to produce limited cellular immunity from T-cells, and only weak protection at the mucosal surfaces, which include the nasal cavity and the stomach.

The reverse is true with oral and nasal vaccines – delivering a vaccine via mucosal surfaces generates mucosal antibodies (IgA) as well as a T-cell response, while systemic antibody response (IgG) can be limited.

A vaccine that could provide a mucosal immune response in the nose and mouth is likely to be preferable against an airborne respiratory virus like SARS-CoV2, as it would provide a barrier at the infection site.

Vaxart and Altimmune have both made progress in the last 12 months for their respective oral and nasal drug delivery platforms, and they see applications for their products across a range of infectious diseases.

A Phase II head-to-head challenge study of Vaxart's oral flu vaccine candidate versus Sanofi's Fluzone shot and a placebo showed superior efficacy to Sanofi's established product. Illness rates were 39% lower in those given Vaxart's oral vaccine compared with unvaccinated subjects, and 27% lower than in those vaccinated with Fluzone.

The trial was funded by the US Biomedical Advanced Research and Development Authority (BARDA) and was published in the Lancet Infectious Diseases in January 2020.

The results also showed that Vaxart's vaccine generated less than one tenth of the serum neutralizing antibodies of the injectable product, yet it protected as well. This illustrated the importance of the T cell immunity, as well as the small but significant levels of mucosal antibodies generated.

Explaining the mechanism on a HC Wainwright & Co investor call in March, Vaxart's founder and chief scientific officer Sean Tucker said: "A little bit of mucosal B-cells goes a long way".

Vaxart's oral formulation VXA-CoV2-1 is based on a non-replicating, Ad5 vector with a TLR3 adjuvant, and targets both the virus's spike (S) and nucleocapsid (N) proteins.

Altimmune's nasal candidate AdCOVID uses a similar approach, also employing a replication-deficient Ad5 viral vector platform.

The company launched its Phase I clinical trial of AdCOVID in February, and expects a data readout in Q2, with an anticipated advanced development program thereafter if the signs are promising.

ALTIMMUNE'S SCOT ROBERTS

Briefing investors at the same online meeting, Altimmune's chief scientific officer Scot Roberts highlighted the promise of its nasal vaccine, which aims to generates mucosal immunity in the nasal cavity and respiratory tract.

"That just can't be generated when you use an intramuscular administration, because it's a local type of immunity that's established where the antigen is presented," he said.

"That's really the best opportunity to both block infection and importantly, block transmission of the virus from an infected individual to others. At the end of the day that's how we're going to bring this pandemic to an end as a walking transmission."

Unlike Vaxart, Altimmune said preclinical studies showed their candidate generated high levels across the three arms of the adaptive immune system, in B-cells, T-cells and mucosal immunity.

Beating Variants Of Concern

Vaxart believes its approach of targeting two of the virus' proteins could be another key differentiator for its vaccine as the N protein is more conserved than the S protein, and therefore could hold out against new SARS-CoV2 variants.

This theory has yet to be clinically tested, but the candidate has passed the first hurdle, with preliminary Phase I trial data meeting its primary and secondary endpoints, with no reports of severe adverse indications.

As in the flu trial, the vaccine generated CD8+ cytotoxic T-cell responses in a majority of patients that may provide long lasting memory, proinflammatory Th1 cytokines and IgA responses, and

elevated mucosal homing receptors for B-cell immune response.

The company is now gearing up for Phase IIa immunogenicity and dose-ranging study in Q2, which once complete, will immediately be followed by a Phase IIb efficacy study.

Vaxart's founder and chief scientific officer Sean Tucker said the world could be stuck on a 'hamster wheel' trying to constantly update injected vaccines that target a mutating S protein.

He believes its approach of targeting the N and S proteins with an oral vaccine could tackle emerging variants of concern.

"The best way to do that is essentially hand out tablets because then you don't have to line up and wait for the syringes to go into people's arms."

Highlighting the benefits of targeting the N protein he said: "The South African strain that everybody's concerned about has only one amino acid difference in the N protein compared to the original Wuhan, so it's again a very well conserved target...for T-cells."

How To Gain Approval?

Vaxart's CEO Andrei Floroiu believes that its best chance of gaining a rapid approval for the vaccine in developed markets like the US and EU is as a booster. This would also allow for smaller study sizes in these regions, an important consideration given that large-scale placebo-controlled trials are no longer feasible given the availability of the first COVID-19 vaccines.

"[We want to] study the potential of our vaccine to boost previously vaccinated and infected [people] We believe we have the potential to show we can do that," said Floroiu. "And then, what better choice for your annual COVID vaccine than a pill?"

Vaxart did not discount the possibility of other placebo-controlled studies in countries such as India, Brazil, or head-to-head studies involving new variants, or even challenge studies.

Last week the company also commissioned market research which suggested its pill could persuade many millions of 'vaccine hesitant' US citizens to change their minds.

Nearly 19 million more American adults – about a third of those now refusing to get vaccinated – would get vaccinated if they could take a pill instead of getting a shot, according to a poll conducted by Quadrant Strategies for the company.

Viral Vector Safety Concerns

As Vaxart, Altimmune and ImmunityBio all use versions of the Ad5 viral vector in their candidates, questions will inevitably arise regarding whether there might be a similar risk of rare

but severe adverse reactions seen in the similar AstraZeneca and J&J adenovirus vector vaccines. (Also see "*With New Rare Blood Clot Warning, J&J COVID-19 Vaccine Rollout Resumes In EU*" - Pink Sheet, 21 Apr, 2021.)

This will also be a question for Oxford University, which last month launched its own Phase I trial, enrolling 30 healthy volunteers in an immunogenicity study of a nasal-delivery formulation of its ChadOx1 based viral vector vaccine, having published *animal studies* in January.

Given the distinct immune response generated by oral and nasal vaccines compared with intramuscular shots, it is not clear if this could be a regulatory concern for these candidates. If the candidates can clear these safety and efficacy hurdles, they just might follow mRNA in being the next big breakthrough in vaccines technology.